# General

## Guideline Title

ACR Appropriateness Criteria® rectal cancer--metastatic disease at presentation.

## Bibliographic Source(s)

Goodman KA, Milgrom SA, Herman JM, Abdel-Wahab M, Azad N, Blackstock AW, Das P, Hong TS, Jabbour SK, Jones WE III, Konski AA, Koong AC, Kumar R, Rodriguez-Bigas M, Small W Jr, Thomas CR Jr, Suh WW, Expert Panel on Radiation Oncology-Gastrointestinal. ACR Appropriateness CriteriaÂ® rectal cancer -- metastatic disease at presentation [online publication]. Reston (VA): American College of Radiology (ACR); 2014. 9 p. [59 references]

## Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Herman J, Messersmith W, Konski AA, Suh WW, Blackstock AW, Cosman BC, Mohiuddin M, Poggi MM, Regine WF, Saltz L, Small W Jr, Zook J, Expert Panel on Radiation Oncology-Rectal/Anal Cancer. ACR Appropriateness Criteria® rectal cancer - metastatic disease at presentation. [online publication]. Reston (VA): American College of Radiology (ACR); 2010. 5 p. [29 references]

# Recommendations

## Major Recommendations

ACR Appropriateness Criteria®

Clinical Condition: Rectal Cancer—Metastatic Disease at Presentation

Variant 1: Initial treatment of a 52-year-old male without a significant past medical history, with an asymptomatic nonobstructing uT3N0 primary rectal tumor 8 cm from the anal verge and a solitary resectable 4-cm metastasis in right lobe of the liver. Karnofsky performance status (KPS) 90.

| Treatment | Rating | Comments |
|---|---|---|
| Initial resection of rectal primary by total mesorectal excision and of the liver lesion (either concurrent or sequential) | 7 | |
| Initial systemic 5-FU-based chemotherapy (FOLFOX/FOLFIRI), then surgery | 7 | Consider anti-EGFR agents with FOLFOX/FOLFIRI in wild-type KRAS tumors. |
| Initial systemic 5-FU-based chemotherapy (FOLFOX/FOLFIRI), | 7 | Consider anti-EGFR agents with FOLFOX/FOLFIRI in wild-type KRAS tumors. |

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

| Treatment | Rating | Comments |
|---|---|---|
| then short-course pelvic RT, then surgery | | |
| Initial systemic 5-FU-based chemotherapy (FOLFOX/FOLFIRI), then long-course chemoradiation, then surgery | 7 | Consider anti-EGFR agents with FOLFOX/FOLFIRI in wild-type KRAS tumors. |
| Initial long-course chemoradiation | 6 | |
| Resection of the liver lesion only | 2 | |
| Best supportive care | 1 | |
| **Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate** | | |

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 2: Initial treatment of a 60-year-old woman without a significant past medical history, with uT3N0 rectal cancer 4 cm from the anal verge causing pain and early symptoms of obstruction, bilobar hepatic metastases (50% liver replacement) and bilateral pulmonary metastases. A colonoscope can be passed through the lesion. KPS 80.

| Treatment | Rating | Comments |
|---|---|---|
| Initial systemic 5-FU-based chemotherapy (FOLFOX/FOLFIRI) | 8 | Consider anti-EGFR agents with FOLFOX/FOLFIRI in wild-type KRAS tumors. |
| Initial long-course chemoradiation | 7 | |
| Initial palliative stent or loop colostomy to relieve obstruction | 5 | Given the low location, diversion may be better due to complications and pain related to stent placement. |
| Initial systemic 5-FU-based chemotherapy (FOLFOX/FOLFIRI plus bevacizumab) | 4 | |
| Initial resection of rectal primary | 3 | |
| Initial palliative pelvic RT alone | 2 | |
| Initial surgical debulking of metastatic disease | 1 | |
| Initial liver directed therapies (transarterial embolization, radiation, RFA) | 1 | |
| Best supportive care | 1 | |
| **Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate** | | |

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 3: Initial treatment of a 60-year-old woman without a significant past medical history, with an asymptomatic, nonobstructing uT3N0 rectal cancer, bilobar hepatic metastases (50% liver replacement) and bilateral pulmonary metastases. KPS 90.

| Treatment | Rating | Comments |
|---|---|---|
| Systemic 5-FU-based chemotherapy (FOLFOX/FOLFIRI ± bevacizumab) ± surgery | 9 | Consider anti-EGFR agents with FOLFOX/FOLFIRI in wild-type KRAS tumors. |
| Systemic 5-FU-based chemotherapy (FOLFOX/FOLFIRI ± bevacizumab) followed by short-course pelvic RT (± surgery) | 6 | Consider anti-EGFR agents with FOLFOX/FOLFIRI in wild-type KRAS tumors. |
| Systemic 5-FU-based chemotherapy (FOLFOX/FOLFIRI ± bevacizumab) | 5 | Consider anti-EGFR agents with FOLFOX/FOLFIRI in wild-type KRAS tumors. |
| **Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate** | | |

| Treatment | Rating | Comments |
|---|---|---|
| followed by long-course chemoradiation (± surgery) | | |
| Best supportive care | 2 | |
| Surgical debulking of metastatic disease | 1 | |
| Resection of rectal primary | 1 | |
| Liver directed therapies (transarterial embolization, radiation, RFA) | 1 | |
| **Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate** | | |

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 4: Initial treatment of a 74-year-old woman with a history of coronary artery disease, severe emphysema, and diabetes, now with an asymptomatic nonobstructing uT3N0 rectal primary cancer with extensive hepatic metastases and abdominal carcinomatosis. KPS 50.

| Treatment | Rating | Comments |
|---|---|---|
| Best supportive care | 8 | |
| Systemic biologic therapy or chemotherapy | 6 | This treatment may be appropriate based on individual patient characteristics. |
| Palliative pelvic RT | 3 | |
| Resection of rectal primary | 1 | |
| Preoperative pelvic RT plus concurrent 5-FU-based chemotherapy | 1 | |
| Resection of metastatic disease | 1 | |
| **Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate** | | |

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Summary of Literature Review

Introduction/Background

According to the American Cancer Society, 40,000 new cases of rectal cancer were diagnosed in the United States in 2014. Approximately 15% of these patients had metastatic disease at presentation. The management of metastatic colorectal cancer (mCRC) has evolved over the past decades with the introduction of improved surgical techniques, radiological and pathological staging, and systemic and radiation therapy (RT) regimens. As a result, the overall survival of mCRC patients has improved significantly in recent years. Furthermore, a small but important group of these patients may potentially be cured of their disease through multimodality management. However, for the majority of mCRC patients, the aim of therapy is to prolong survival and palliate symptoms.

Management of patients with newly diagnosed metastatic rectal cancer (mRC) may be complex, and treatment decisions benefit from multidisciplinary input. Management must be individualized based on the overall medical condition of the patient, the extent and distribution of metastatic disease, and the patient's wishes.

Management of the Primary Tumor

The optimal management of the primary tumor in patients with metastatic disease is controversial; however, the paradigm is changing with the substantial improvements in systemic therapy and the expected duration of survival. Given the potential for cure after resection of all locoregional and distant disease, the approach to the primary tumor is determined by the resectability of the metastatic lesions as well as the severity of symptoms from the primary rectal mass.

Resectable Metastatic Disease

After resection of the primary tumor and distant metastases, mCRC patients may experience long-term survival, and a small subset may be cured. Therefore, aggressive surgical management is warranted.

Metastatic patients with low-volume, stage T1-T2N0, or high rectal primary tumors may be ideally treated with upfront resection of the primary

tumor and metastases or with preoperative chemotherapy alone followed by a synchronous or staged resection of the primary tumor and metastases. On the other hand, patients with T3-4, regional node-positive or low-lying primary tumors should be considered for preoperative combined-modality therapy (CMT) with 5-fluoruracil (5-FU) and pelvic RT to reduce the risk of pelvic recurrence. Although limited data exist to support this approach in mRC, the improved local control and decreased toxicity with preoperative versus postoperative CMT may be extrapolated from the data in locally advanced rectal cancer. In the United States, long-course chemoradiation (50.4 Gy in 28 fractions) is the standard preoperative management of rectal cancer; however, short-course RT (25 Gy in 5 fractions) may be considered in mRC to reduce the delay before surgery and initiation of full-dose systemic therapy. Any patient with an obstructing tumor should undergo surgical diversion prior to initiating CMT, regardless of the fractionation schedule used. A less preferable option for these patients would be endoscopic placement of a rectal stent.

Patients who have undergone upfront complete resection of both the primary tumor and all known metastatic disease can be considered candidates for the postoperative management routinely provided in stage II or III rectal cancer, which may include adjuvant chemotherapy with or without chemoradiation based on the stage and location of the primary tumor. Postoperative CMT should be strongly considered for any patient with T4 disease who did not receive preoperative pelvic RT.

Unresectable Metastatic Disease

The primary management of unresectable metastatic disease is chemotherapy. In the majority of cases, initiation of chemotherapy should not be postponed in favor of local therapy given the high response rates and infrequency of rapid progression through first-line regimens. One important exception is obstructed patients, who require immediate diversion.

As with all scenarios, however, care plans must be individualized to the particular needs of the patient based on the pattern and pace of metastatic disease, degree of symptoms, risk of imminent obstruction, and comorbidities. For example, patients with a low burden of metastatic disease, a bulky rectal tumor, and a high likelihood of long-term survival may benefit from treatment of the primary tumor to prevent symptoms from progressive or recurrent pelvic disease. Since preoperative CMT followed by resection may be the most effective approach for controlling the rectal primary, these patients may be appropriately treated with this regimen. Alternatively, chemotherapy may be provided upfront, and patients who achieve a favorable response may subsequently be treated with consolidative CMT and surgery to provide local control. On the other hand, patients with high-volume metastases and a small, asymptomatic rectal tumor are likely to die of their systemic disease before the primary tumor causes significant symptoms. In such patients, systemic chemotherapy is usually most appropriate, with local pelvic therapy reserved for palliation, if needed.

Management of Liver Metastases

The liver is the most frequent and often the only site of metastasis in CRC. Complete surgical resection of liver metastases can improve survival to an impressive 40% at 5 years and 25% at 10 years. Therefore, patients who are operative candidates, have resectable liver metastases, and have minimal or resectable extrahepatic disease should be directed to surgery. Such patients may undergo either a staged or synchronous resection of the metastases and primary rectal tumor. There is no consensus regarding the best sequence; rather, institutional philosophy tends to guide management. The classic approach is surgical removal of the primary tumor, which is considered to be the nidus of metastatic disease, followed by chemotherapy and a second surgery to remove the liver metastases at a later date. If patients progress while on chemotherapy between the 2 surgeries, the second surgery may not be performed. This approach may be most appropriate for patients who are symptomatic from their primary tumor. Evidence to support this classic approach suggests that the primary tumor affects the liver to promote angiogenesis and metastasis. A synchronous resection of primary tumor and liver metastases obviates the need for 2 separate operations, but the more arduous surgery may not be suitable for patients with a poor performance status. A more contemporary approach, commonly referred to as "liver-first," is initial excision of the liver metastasis, which demonstrates the genetic mutations and capacity to metastasize, then later resection of the local tumor. Frequently, the primary rectal disease is locally advanced, warranting neoadjuvant CMT; in select patients with a complete clinical response, close observation may delay or abrogate the need for rectal surgery. In addition to resection of the primary tumor and liver metastases, systemic chemotherapy improves disease-free and progression-free survival. Administration of chemotherapy before or after hepatectomy results in equivalent disease-free and overall survival.

Unfortunately, 70% to 80% of patients with CRC liver metastases are not candidates for resection at initial presentation. Upfront management of patients with unresectable metastases is chemotherapy. Primarily unresectable liver metastases may become resectable after responding to chemotherapy. Portal vein embolization or hepatic arterial infusion with floxuridine/dexamethasone may increase the rates of conversion to resectability and thus improve long-term survival. For tumors that remain unresectable, nonsurgical liver-directed therapies have yielded promising results and may be considered. For example, high-dose stereotactic body RT is well tolerated and provides local control rates of ≥77% at 1 year. Radiofrequency ablation (RFA) yields excellent local control of small (<3 cm) CRC liver metastases. Radioembolization, using yttrium-90 microspheres in combination with systemic therapy, results in a greater reduction in hepatic metastases than treatment with systemic therapy alone. The addition of chemoembolization or cryotherapy to chemotherapy may also improve outcomes and is the topic of ongoing study (see Variant 1

and Variant 2 above).

Cytotoxic and Targeted Therapies

5-FU has been the basis of standard chemotherapy for treating CRC for the last five decades. Continuous infusion schedules have replaced bolus regimens because they were shown to be more effective and less toxic. Capecitabine, an oral fluoropyrimidine, may be used in place of intravenous 5-FU. Capecitabine is associated with superior response rates and a lower incidence of adverse events, but no significant survival differences are observed when compared to bolus 5-FU/leucovorin (LV). Capecitabine has a dose-limiting toxicity of hand-foot syndrome, which appears to be more common in the U.S. population than in Europe, where most of the studies were conducted. In addition, capecitabine requires a highly motivated and reliable patient who will take oral medication correctly, will not miss or duplicate doses, and will hold medications at appropriate levels of toxicity.

Combining 5-FU/LV or capecitabine with newer agents, including irinotecan and oxaliplatin, has resulted in improved outcomes. Irinotecan, a topoisomerase I inhibitor, can be used independently in 5-FU-resistant advanced CRC, or can be combined with 5-FU/LV as first-line therapy in patients with metastatic disease. Oxaliplatin, a third-generation platinum compound, has been shown to be a superior regimen to bolus 5-FU/irinotecan regimens. FOLFOX (5-FU/LV/oxaliplatin), FOLFIRI (5-FU/LV/irinotecan), or FOLFOXIRI (5-FU/LV/oxaliplatin/irinotecan) are acceptable first-line regimens to treat mCRC in patients appropriate for intensive therapy. In patients receiving CMT, the addition of oxaliplatin to 5-FU and RT increases toxicity without improving primary tumor response rates, as shown in 3 randomized controlled trials: STAR-01, ACCORD, and NSABP R-04. In the metastatic setting, sequential therapy with multiagent chemotherapy before and/or after 5-FU-based CMT is an option to control systemic disease.

New "targeted" therapies such as cetuximab, panitumumab, and bevacizumab have increased the options available for treating metastatic disease. Cetuximab and panitumumab are monoclonal antibodies directed against the epidermal growth factor receptor (EGFR). Cetuximab received U.S. Food and Drug Administration (FDA) approval for treatment of irinotecan-resistant disease, in which a 22% response rate was associated with cetuximab/irinotecan therapy versus 11% with cetuximab as a single agent. Panitumumab was FDA-approved after demonstrating improved progression-free survival versus best supportive care in patients with chemotherapy-refractory disease. The discovery that patients with KRAS-mutated tumors do not derive benefit from EGFR-targeted agents has ushered an era of "personalized" therapy in CRC. For instance, in the large CO.17 study of cetuximab versus best supportive care in chemotherapy-resistant advanced CRC, patients harboring a KRAS mutation had a response rate of 1% and median overall survival time (mOS) of 4.5 months, whereas those who had KRAS wild-type tumors had a response rate of 13% and mOS of 9.5 months. In a retrospective meta-analysis of the CRYSTAL and OPUS studies, the addition of cetuximab to chemotherapy resulted in a significant improvement in progression-free and overall survival times in patients with KRAS wild-type tumors. Conversely, in a phase III study (COIN) comparing cetuximab in combination with capecitabine or intravenous 5-FU and oxaliplatin versus chemotherapy alone as first-line treatment in mCRC, the former did not meet its primary endpoint of overall survival in KRAS wild-type patients (17 months versus 17.9 months; HR 1.04; 95% confidence interval [CI] 0.90-1.20; $P$=0.68). Two recent studies, OPUS and PRIME, demonstrated a progression-free survival benefit with the addition of cetuximab or panitumumab, respectively, to FOLFOX in the first-line setting; however, no benefit was shown for patients with KRAS mutations. These studies collectively suggest that EGFR inhibitors should be considered in treating KRAS wild-type tumors, but should not be offered in KRAS mutant patients. Furthermore, emerging data suggest that KRAS wild-type mCRC patients receiving FOLFIRI and cetuximab as a first-line treatment experience improved overall survival when compared to those receiving FOLFIRI and bevacizumab.

Bevacizumab is a monoclonal antibody directed against the vascular endothelial growth factor. In a randomized phase III trial, adding bevacizumab to bolus 5-FU/LV/irinotecan in patients with advanced CRC improved overall survival by 4.5 months. However, in a larger phase III trial of oxaliplatin-based first-line chemotherapy, the addition of bevacizumab resulted in a modest but significant improvement in progression-free survival, but no improvement in response rate and no significant impact on survival. In addition, although there were promising initial results with "double biologic" strategies of combining bevacizumab and EGFR-targeting monoclonal antibodies, both the PACCE (panitumumab) and CAIRO2 (cetuximab) trials showed shorter survival times and greater toxicity in the arms with double biologics. Thus, bevacizumab should not be combined with other biologic agents but may be used in combination with chemotherapy to treat mCRC. Based on work in animal models, there is concern that administration of an antiangiogenic preoperatively may increase the risk of surgical complications. However, multiple groups have retrospectively shown that surgeries, including liver resections, are safe after bevacizumab delivery. Delaying an elective operation until 6 to 8 weeks (2–3 bevacizumab half-lives) after treatment with bevacizumab is a reasonable consensus practice.

Researchers continue to investigate the role of new targeted therapies in the management of mCRC. Recently, some of these agents have been shown to provide small but statistically significant survival benefits. For example, addition of aflibercept to FOLFIRI resulted in a mOS of 13.5 months versus 12.06 months with FOLFIRI and placebo. In a study of patients whose mCRC had progressed on standard therapy, treatment with regorafenib yielded a mOS of 6.4 months versus 5.0 months in the placebo group. These and other new targeted agents may play an increasing role in the management of mCRC. Clinical trials should be considered for patients with a good performance status with the goal of developing

more effective therapeutic regimens and rational combinations of chemotherapy, targeted agents, and radiotherapy for metastatic rectal cancer (see Variant 3 above).

Supportive Care

Patients with widespread unresectable mCRC, poor performance status, and multiple comorbidities are often best managed with supportive, comfort-oriented intent. The goals of care should be made clear to these patients, the majority of whom may not understand that their cancer is incurable and that treatment is intended to provide palliation only. Local therapies may be valuable for symptomatic relief. For example, palliative RT or CMT achieves at least temporary relief in 80% of mCRC patients suffering from pain, bleeding, or obstruction, with more durable palliation provided by doses of ≥40 Gy. Stents may also be used to palliate obstruction but may be poorly tolerated in the distal rectum (see Variant 4 above).

Summary

- Survival of mCRC patients has improved significantly in recent years.
- Management of mRC patients benefits from multidisciplinary input.
- Operative candidates with resectable metastatic disease should undergo resection of the primary tumor and metastases and should receive chemotherapy.
- Pelvic irradiation with concurrent 5-FU prior to resection of the rectal tumor is appropriate in patients with bulky, low-lying primary tumors, limited metastatic disease, and a long life expectancy.
- Patients with unresectable metastases should receive upfront chemotherapy.
- Multiple nonsurgical therapies are available to target unresectable liver metastases.
- A combination of cytotoxic and targeted systemic therapies is used in metastatic colorectal cancer and has significantly improved outcomes.
- Patients with widespread disease, poor performance status, or multiple comorbidities may be best managed with comfort-oriented, supportive care.

Abbreviations

- EGFR, epidermal growth factor receptor
- 5-FU, 5-fluorouracil
- FOLFOX, folinic acid (leucovorin), 5-fluorouracil, and oxaliplatin
- FOLFIRI, folinic acid (leucovorin), 5-fluorouracil, and irinotecan
- RFA, radiofrequency ablation
- RT, radiation therapy
- TNM, tumor, node, metastasis

## Clinical Algorithm(s)

Algorithms were not developed from criteria guidelines.

# Scope

## Disease/Condition(s)

Rectal cancer with metastatic disease

## Guideline Category

Management

Treatment

## Clinical Specialty

Colon and Rectal Surgery

Gastroenterology

Internal Medicine

Oncology

Radiation Oncology

Surgery

## Intended Users

Health Plans

Hospitals

Managed Care Organizations

Physicians

Utilization Management

## Guideline Objective(s)

To evaluate the appropriateness of therapeutic procedures for rectal cancer with metastatic disease

## Target Population

Patients with rectal cancer and metastatic disease at presentation

## Interventions and Practices Considered

1. Surgery
    - Resection of rectal primary tumor by total mesorectal excision and of the liver lesion (concurrent or sequential)
    - Resection of the liver lesion only
    - Surgical debulking of metastatic disease
    - Resection of rectal primary tumor
2. Systemic 5-fluororuracil (5-FU)-based chemotherapy: FOLFOX (folinic acid [leucovorin], 5-fluorouracil, and oxaliplatin) or FOLFIRI (folinic acid [leucovorin], 5-fluorouracil, and irinotecan)
    - Followed by surgery
    - Followed by short-course pelvic radiotherapy (RT), then surgery
    - Followed by long-course chemoradiation, then surgery
    - Systemic 5-FU-based chemotherapy (FOLFOX/FOLFIRI plus bevacizumab)
    - Systemic 5-FU-based chemotherapy (FOLFOX/FOLFIRI ± bevacizumab) ± surgery
    - Systemic 5-FU-based chemotherapy (FOLFOX/FOLFIRI ± bevacizumab) followed by short-course pelvic RT (± surgery)
    - Systemic 5-FU-based chemotherapy (FOLFOX/FOLFIRI ± bevacizumab) followed by long-course chemoradiation (± surgery)
3. Systemic biologic therapy or chemotherapy
4. Palliative pelvic RT alone
5. Preoperative pelvic RT plus concurrent 5-FU-based chemotherapy
6. Long-course chemoradiation
7. Liver-directed therapies (transarterial embolization, radiation, radiofrequency ablation [RFA])
8. Palliative stent or loop colostomy to relieve obstruction
9. Best supportive care

## Major Outcomes Considered

- Progression-free survival rate
- Overall survival rate
- Progression-free and overall survival times
- Disease-free survival
- Response rate
- Adverse effects of treatment
- Postoperative mortality and morbidity

# Methodology

## Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

Literature Search Procedure

Staff search in PubMed only for peer reviewed medical literature for routine searches. Any article or guideline may be used by the author in the narrative but those materials may have been identified outside of the routine literature search process.

The Medline literature search is based on keywords provided by the topic author. The two general classes of keywords are those related to the condition (e.g., ankle pain, fever) and those that describe the diagnostic or therapeutic intervention of interest (e.g., mammography, MRI).

The search terms and parameters are manipulated to produce the most relevant, current evidence to address the American College of Radiology Appropriateness Criteria (ACR AC) topic being reviewed or developed. Combining the clinical conditions and diagnostic modalities or therapeutic procedures narrows the search to be relevant to the topic. Exploding the term "diagnostic imaging" captures relevant results for diagnostic topics.

The following criteria/limits are used in the searches.

1. Articles that have abstracts available and are concerned with humans.
2. Restrict the search to the year prior to the last topic update or in some cases the author of the topic may specify which year range to use in the search. For new topics, the year range is restricted to the last 10 years unless the topic author provides other instructions.
3. May restrict the search to Adults only or Pediatrics only.
4. Articles consisting of only summaries or case reports are often excluded from final results.

The search strategy may be revised to improve the output as needed.

## Number of Source Documents

The total number of source documents identified as the result of the literature search is not known.

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

Study Quality Category Definitions

Category 1 - The study is well-designed and accounts for common biases.

Category 2 - The study is moderately well-designed and accounts for most common biases.

Category 3 - There are important study design limitations.

Category 4 - The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:

a. The study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description).
b. The study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence.
c. The study is an expert opinion or consensus document.

## Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

The topic author drafts or revises the narrative text summarizing the evidence found in the literature. American College of Radiology (ACR) staff draft an evidence table based on the analysis of the selected literature. These tables rate the strength of the evidence (study quality) for each article included in the narrative text.

The expert panel reviews the narrative text, evidence table, and the supporting literature for each of the topic-variant combinations and assigns an appropriateness rating for each procedure listed in the table. Each individual panel member assigns a rating based on his/her interpretation of the available evidence.

More information about the evidence table development process can be found in the ACR Appropriateness Criteria® Evidence Table Development document (see the "Availability of Companion Documents" field).

## Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

## Description of Methods Used to Formulate the Recommendations

Rating Appropriateness

The appropriateness ratings for each of the procedures included in the Appropriateness Criteria topics are determined using a modified Delphi methodology. A series of surveys are conducted to elicit each panelist's expert interpretation of the evidence, based on the available data, regarding the appropriateness of an imaging or therapeutic procedure for a specific clinical scenario. American College of Radiology (ACR) staff distribute surveys to the panelists along with the evidence table and narrative. Each panelist interprets the available evidence and rates each procedure. The surveys are completed by panelists without consulting other panelists. The appropriateness rating scale is an ordinal scale that uses integers from 1 to 9 grouped into three categories: 1, 2, or 3 are in the category "usually not appropriate"; 4, 5, or 6 are in the category "may be appropriate"; and 7, 8, or 9 are in the category "usually appropriate." Each panel member assigns one rating for each procedure for a clinical scenario. The ratings assigned by each panel member are presented in a table displaying the frequency distribution of the ratings without identifying which members provided any particular rating.

If consensus is reached, the median rating is assigned as the panel's final recommendation/rating. Consensus is defined as eighty percent (80%) agreement within a rating category. A maximum of three rounds may be conducted to reach consensus. Consensus among the panel members must be achieved to determine the final rating for each procedure.

If consensus is not reached, the panel is convened by conference call. The strengths and weaknesses of each imaging procedure that has not

reached consensus are discussed and a final rating is proposed. If the panelists on the call agree, the rating is proposed as the panel's consensus. The document is circulated to all the panelists to make the final determination. If consensus cannot be reached on the call or when the document is circulated, "No consensus" appears in the rating column and the reasons for this decision are added to the comment sections.

This modified Delphi method enables each panelist to express individual interpretations of the evidence and his or her expert opinion without excessive influence from fellow panelists in a simple, standardized and economical process. A more detailed explanation of the complete process can be found in additional methodology documents found on the ACR Web site (see also the "Availability of Companion Documents" field).

### Rating Scheme for the Strength of the Recommendations

Not applicable

### Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

### Method of Guideline Validation

Internal Peer Review

### Description of Method of Guideline Validation

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The recommendations are based on analysis of the current literature and expert panel consensus.

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

Selection of appropriate treatment procedures for patients with newly diagnosed metastatic rectal cancer

### Potential Harms

- Based on work in animal models, there is concern that administration of an antiangiogenic preoperatively may increase the risk of surgical complications.
- Capecitabine has a dose-limiting toxicity causing hand-foot syndrome, which appears to be more common in the U.S. population than in Europe, where most of the studies were conducted. In addition, capecitabine requires a highly motivated and reliable patient who will take oral medication correctly, will not miss or duplicate doses, and will hold medications at appropriate levels of toxicity.
- The addition of oxaliplatin to 5-fluorouracil (5-FU) and radiation therapy (RT) increases toxicity without improving primary tumor response rates.
- Stent placement is associated with pain and surgical complications.

# Qualifying Statements

## Qualifying Statements

The American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

# Implementation of the Guideline

## Description of Implementation Strategy

An implementation strategy was not provided.

# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

End of Life Care

Living with Illness

## IOM Domain

Effectiveness

# Identifying Information and Availability

## Bibliographic Source(s)

Goodman KA, Milgrom SA, Herman JM, Abdel-Wahab M, Azad N, Blackstock AW, Das P, Hong TS, Jabbour SK, Jones WE III, Konski AA, Koong AC, Kumar R, Rodriguez-Bigas M, Small W Jr, Thomas CR Jr, Suh WW, Expert Panel on Radiation Oncology-Gastrointestinal. ACR Appropriateness CriteriaÂ® rectal cancer -- metastatic disease at presentation [online publication]. Reston (VA): American College of Radiology (ACR); 2014. 9 p. [59 references]

## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2007 (revised 2014)

## Guideline Developer(s)

American College of Radiology - Medical Specialty Society

## Source(s) of Funding

The American College of Radiology (ACR) provided the funding and the resources for these ACR Appropriateness Criteria®.

## Guideline Committee

Committee on Appropriateness Criteria, Expert Panel on Radiation Oncology–Gastrointestinal

## Composition of Group That Authored the Guideline

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## Financial Disclosures/Conflicts of Interest

Not stated

## Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Herman J, Messersmith W, Konski AA, Suh WW, Blackstock AW, Cosman BC, Mohiuddin M, Poggi MM, Regine WF, Saltz L, Small W Jr, Zook J, Expert Panel on Radiation Oncology-Rectal/Anal Cancer. ACR Appropriateness Criteria® rectal cancer - metastatic disease at presentation. [online publication]. Reston (VA): American College of Radiology (ACR); 2010. 5 p. [29 references]

## Guideline Availability

Electronic copies: Available from the American College of Radiology (ACR) Web site .

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

## Availability of Companion Documents

The following are available:

- ACR Appropriateness Criteria®. Overview. Reston (VA): American College of Radiology; 2013 Nov. 3 p. Electronic copies: Available from the American College of Radiology (ACR) Web site .
- ACR Appropriateness Criteria®. Literature search process. Reston (VA): American College of Radiology; 2013 Apr.1 p. Electronic copies: Available from the ACR Web site .
- ACR Appropriateness Criteria®. Evidence table development – diagnostic studies. Reston (VA): American College of Radiology; 2013

Nov. 3 p. Electronic copies: Available from the ACR Web site .

- ACR Appropriateness Criteria®. Evidence table development – therapeutic studies. Reston (VA): American College of Radiology; 2013 Nov. 4 p. Electronic copies: Available from the ACR Web site .
- Appropriateness Criteria® rectal cancer—metastatic disease at presentation. Evidence table. American College of Radiology; 2014. 26 p. Electronic copies: Available from the ACR Web site .

## Patient Resources

None available

## NGC Status

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